

PET Study of the Human Foveal Fixation System

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Abstract: Positron emission tomography (PET) was used to investigate the functional anatomy of the foveal fixation system in 10 subjects scanned under three different conditions: at rest (REST), during the fixation of a central point (FIX), and while fixating the same foveal target during the presentation of peripheral visual distractors (DIS). Compared with the REST condition, both FIX and DIS tasks activated a common set of cortical areas. First, in addition to the involvement of the occipital visual cortex, both the frontal eye field (FEF) and the intraparietal sulcus (IPS) were bilaterally activated. Right frontal activation was also found in the dorsolateral prefrontal cortex, the inferior part of the precentral gyrus, and the inferior frontal gyrus. These results suggest that both FEF and IPS may constitute the main cortical regions subserving bilaterally the foveal fixation system in humans. The remaining right frontal activations may be considered as part of the anterior attentional network, supporting a role for the right frontal lobe in the allocation of the attentional mechanisms. Compared with the FIX condition, the DIS task also revealed the perceptual and cognitive processes related to the presence of peripheral visual distractors during foveal fixation. In addition to a bilateral activation of the V5/MT motion-sensitive area, a right FEF-IPS network was activated which may correspond to the engagement of the visuospatial attention. Finally, normalized regional cerebral blood flow (NrcBF) decreases were also observed during both DIS and FIX condition performance. Such NrcBF decreases were centered in the superior and middle temporal gyri, the prefrontal cortex, and the precuneus and the posterior retrosplenial part of the cingulate gyrus. *Hum. Brain Mapping* 8:28–43, 1999. © 1999 Wiley-Liss, Inc.

Key words: PET; NrcBF; REST

INTRODUCTION

Eye movements and the intervening periods of visual fixation represent a simple behavioral system in humans. Saccades move the eyes rapidly from one point of interest to another, but little visual information is available during these movements, which usually last no more than 40 msec. It is during the periods of fixation

following saccades that we obtain nearly all visual information. Voluntary fixation on a stationary visual target consists of an ocular stabilization process, which ensures that the target's image is held in the retina's area of highest visual acuity, namely, the fovea [Ott et al., 1992].

Knowledge about the existence of a foveal fixation system in man has come primarily from human clinico-pathologic studies. Balint's original patient with his eponymous syndrome showed an ocular fixation deficit associated with peripheral visual attention disorders and a paucity of eye movements in relation to bilateral parieto-occipital lesions [Balint, 1909]. Lesions damaging the frontal cortex result in impaired fixation ability [Holmes, 1938; Guitton et al., 1985; Paus et al., 1991], while the locking of fixation due to restriction of

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attention to the fovea was observed in cases of parietal lesions [Hecaen and De Ajuriaguerra, 1954; Pierrot-Deseilligny et al., 1986]. These previous studies point towards a close relationship between fixation, eye movements, and visuospatial attention in humans.

The functional anatomy of saccadic eye movements has been investigated in normal subjects to describe the cortical and subcortical regions involved in various types of saccade, using positron emission tomography (PET) [Fox et al., 1985; Petit et al., 1993, 1996a; Paus et al., 1993; Nakashima et al., 1994; Lang et al., 1994; Anderson et al., 1994; O'Driscoll et al., 1995; O'Sullivan et al., 1995; Sweeney et al., 1996; Law et al., 1997, 1998] and functional magnetic resonance imaging (fMRI) [Darby et al., 1996; Petit et al., 1997a; Luna et al., 1998; Corbetta et al., 1998]. Other functional imaging studies have isolated the different components of human visual attention systems [PET: Pardo et al., 1990, 1991; Corbetta et al., 1991, 1993, 1995; Gitelman et al., 1996; Coull et al., 1996; Nobre et al., 1997; fMRI: Rosen et al., 1997; Corbetta, 1998; Corbetta et al., 1998].

In contrast, little attempt has been made to explore the network of regions involved in foveal fixation. In a previous study, we showed that the fixation of a recall central target in total darkness compared to a rest condition activated the frontal eye fields (FEF), the supplementary eye fields (SEF), and the median cingulate gyrus [Petit et al., 1995]. Additional results demonstrating a prefrontal normalized regional cerebral blood flow (NrCBF) increase have been reported indirectly when a central fixation condition was compared to the execution of visually guided saccades [Anderson et al., 1994; Sweeney et al., 1996].

The goal of the present study was to investigate, using PET, the functional anatomy of the foveal fixation system and its relationship to the system for visuospatial attention in healthy humans. We studied the structures involved during simple fixation of a central point, and during fixation of the same point while distractive peripheral visual targets appeared randomly on either side of the central target. This second fixation task was designed to limit spontaneous eye movements. This was done by asking the subjects to fixate the central point and to disregard the peripheral visual distractors. The present data appeared previously in abstract form [Petit et al., 1997b].

METHODS

Subjects

Ten healthy 22–34-year-old right-handed young male adults (S1–S10, mean age 24.3 ± 4.1 years) participated in this study. All were right-handed as assessed by the

Edinburgh questionnaire [Oldfield, 1971] and were free of brain abnormalities as judged by their T1-weighted high-resolution magnetic resonance image (MRI) brain scan. Approval of these experiments was given by an Ethics Committee, and informed written consent was obtained from each subject after the procedures had been fully explained.

Tasks

Three different tasks were used in this study. In the first task, a baseline control condition (REST), subjects were asked to avoid moving their eyes while resting in total darkness with their eyes open. In the second task, a simple foveal fixation condition (FIX), subjects were asked to fixate a red light-emitting diode (LED) that appeared at the primary central eye position 30 sec before the ^{15}O -labeled water injection and for 110 sec, i.e., until the end of data acquisition. In the third task, a foveal fixation condition with peripheral distractors (DIS), subjects fixated the same central LED while distractive peripheral visual targets appeared randomly on either side of the central point. Thirty seconds before the ^{15}O -labeled water injection, the subjects started to fixate the central fixation point, while consecutive red LEDs appeared for 500 msec at different peripheral locations of the horizontal visual meridian until the end of the data acquisition. The subjects were explicitly instructed to fixate the central point and to disregard the peripheral visual distractors. Thus, spontaneous saccadic eye movements had to be inhibited to maintain fixation at the central point, which possibly increased the locking of gaze and the attentional load at the central point. During the three conditions, the subjects were allowed to blink as much as they wanted. The visual display consisted of a horizontal array of 30 red LEDs arranged symmetrically from $1\text{--}15^\circ$ on both sides of the central point and spaced out 1° one from another. The size of each LED was 0.125° of the visual field. In order to ascertain that no spontaneous eye movements were executed during the different tasks, horizontal electrooculograms (EOG) were recorded for 5 subjects (S1–S5), using surface electrodes placed at the outer canthi and at the right ear as a reference. The EOG system had a resolution superior to 1° of visual angle and was calibrated before each condition. All EOG records were analyzed by computer, using a dedicated software (SAMO) [Denise et al., 1996] which detects saccadic components and quantifies the amplitude and frequency of the spontaneous saccadic eye movements.

Since fixation of a remembered central point produces activation of frontal structures [Petit et al., 1995],

REST conditions were always run first. This was done so that the subjects would not use the fixation point information as a strategy to keep their eyes still during the REST condition. After the REST conditions, the order of FIX and DIS conditions was counterbalanced across individuals. The horizontal LED array was located at the back of the PET tomograph, and the subjects could see the targets with the help of a mirror placed in front of their eyes. A black chamber was set up around the PET tomograph, the horizontal LEDs array, and the subject so that all PET measures were done in total darkness during the REST condition or in partial darkness during both FIX and DIS conditions.

Data acquisition

Two different PET cameras in different PET centers were used for NrCBF measurement.

For the first 5 subjects (S1–S5), NrCBF was monitored by PET and ^{15}O -labeled water six times in each subject, replicating each of the three conditions, i.e., REST, DIS, and FIX. For each condition, 31 contiguous brain slices were acquired simultaneously on an ECAT 953B/31 PET camera, giving an in-plane resolution of 5 mm [Mazoyer et al., 1991]. Emission data were acquired with septa extended. Following the intravenous bolus injection of 60 mCi of ^{15}O -labeled water, a single 80-sec scan was reconstructed (including a correction for head attenuation using a measured transmission scan) with a Hanning filter of 0.5 mm^{-1} and displayed with a voxel size of $2 \times 2 \times 3.375\text{ mm}$. The interval between injections was 15 min. In addition to the PET data, axial and sagittal series of 3-mm-thick T1-weighted high-resolution magnetic resonance images (MRI) covering the whole brain were acquired for each subject on a 0.5 Tesla GE-MRMAX imager.

For the other 5 subjects (S6–S10), NrCBF was measured six times in one subject and 12 times in the 4 other subjects, replicating and quadrupling the series of the three conditions, respectively. For each rCBF measurement, 47 contiguous brain slices were acquired simultaneously on an ECAT-Exact-HR PET camera, giving an in-plane resolution of 3.7 mm [Wienhard et al., 1994]. Emission data were acquired with septa retracted. Following the intravenous bolus injection of 20 mCi of ^{15}O -labeled water, a single 60-sec scan was reconstructed (including a correction for head attenuation using a measured transmission scan), with a Hanning filter of 0.25 mm^{-1} and displayed with a voxel size of $2 \times 2 \times 3.125\text{ mm}$. The interval between injections was 15 min. In addition to the PET data, axial series of 2-mm-thick T1-weighted high-resolu-

tion MRI covering the whole brain were acquired for each subject on a 0.5 Tesla Philips Gyroscan imager.

Data analysis

The question of reproducibility, reliability, and comparability of the data acquired in different PET centers was recently investigated [Poline et al., 1996]. That study showed that data from different PET centers can be pooled to improve the reliability of results. Therefore, statistical parametric maps (SPM) were generated for our full group of 10 subjects to compare the DIS, FIX, and REST conditions using the three-dimensional version of SPM [Friston et al., 1995]. The original brain images were transformed into the standard stereotactic Talairach space [Talairach and Tournoux, 1988]. Global differences in the cerebral blood flow (CBF) differences within and between subjects were covaried out, and comparisons across conditions were made by way of t-statistics [Friston et al., 1991, 1994]. After alignment in stereotactic space, the number of resels was 161 for each comparison, with a voxel of $2 \times 2 \times 4\text{ mm}$. Each comparison was performed on a common volume of 161 resels, limited to slices located from -32 – $+52\text{ mm}$ in the z direction of the stereotactic space, with a smoothness of $16.7 \times 19.0 \times 20.5\text{ mm}$. For each comparison, the t-map was transformed to a Z-map. The threshold for statistical significance was set at $Z = 3.1$, which corresponds to a 0.001 confidence level (without correction for multiple comparisons).

The experiment was designed to use both the REST and the FIX conditions as reference conditions. Thus, significant NrCBF increases as compared to the resting control condition (DIS vs. REST, FIX vs. REST) were taken to indicate activation due to processes shared by both tasks. Significant differences between fixation conditions (DIS vs. FIX) were then taken to indicate the areas that were specifically related to the presence of peripheral visual distractors. We also report significant NrCBF decreases revealed by the REST vs. DIS comparison and the REST vs. FIX comparison. The coordinates and the spatial extent of activated areas are given in Tables I–V.

RESULTS

EOG analysis

For the first 5 subjects (S1–S5), EOG recordings for each PET data acquisition were usable for processing. The average amplitude of spontaneous horizontal saccadic eye movements during REST, FIX, and DIS conditions were $2.6 \pm 2.5^\circ$ (mean \pm SD), $1.9 \pm 0.9^\circ$, and

TABLE I. Foci of significant NrCBF increases in the DIS condition as compared with the REST condition†

Activated areas	Area size	Coordinates			Δ NrCBF	Z score
		x	y	z		
L. inferior occipital gyrus	6,265 (1)	-30	-90	-12	14.0	8.2
R. inferior occipital gyrus	Part of (1)	26	-90	-8	14.9	8.6
L. middle occipital gyrus	Part of (1)	-36	-70	-8	7.8	6.4
R. middle occipital gyrus	Part of (1)	38	-76	-4	8.7	6.8
L. precentral gyrus (superior part)	41	-36	-6	40	2.7	3.2
R. precentral gyrus (superior part)	334 (2)	34	-10	48	3.4	3.7
R. precentral gyrus (inferior part)	Part of (2)	48	2	28	3.1	4.4
R. middle frontal gyrus	76	32	44	28	3.1	3.4
L. intraparietal sulcus	28	-24	-70	40	2.8	2.8*
R. intraparietal sulcus	Part of (1)	22	-68	44	5.6	4.9

† The data, based on 10 subjects, are local maxima detected with the three-dimensional version of SPM (see Methods). Activated region volume is given in number of voxels. Within these regions, the anatomical localization of the maximum Z scores of the voxels is given on the basis of the atlas of Talairach and Tournoux [1988], using their stereotactic coordinates in mm (R., right; L., left). Uncorrected significance level was set at $P < 0.001$ (Z score > 3.1). Δ NrCBF (in %) is the local blood flow variations between the two compared conditions. * Not significant at voxel Z threshold of 3.1.

$1.8 \pm 1.2^\circ$, respectively. No significant differences between REST, FIX, and DIS were observed in term of amplitude (post hoc t-test, $P > 0.05$).

The average number of spontaneous saccadic eye movements during REST, FIX, and DIS conditions were 33 ± 22 , 10 ± 9 , and 7 ± 7 , respectively. The difference between REST and FIX as well as between REST and DIS was significant (post hoc t-test, $P > 0.05$). No significant differences between FIX and DIS were observed (post hoc t-test, $P < 0.05$).

This analysis of EOG recordings showed that the subjects were able to effectively maintain central fixa-

tion during both DIS and FIX conditions. Fewer and smaller spontaneous saccadic eye movements were executed during both DIS and FIX conditions than during the baseline REST condition, which indicates that regional activations reported in this study are unlikely to be related to saccades occurring during fixation tasks.

SPM analysis

As indicated above, five comparisons were performed in both groups. DIS vs. REST, FIX vs. REST,

TABLE II. Foci of significant NrCBF increases in the FIX condition as compared with the REST condition†

Activated areas	Area size	Coordinates			Δ NrCBF	Z score
		x	y	z		
L. inferior occipital gyrus	3,948 (1)	-32	-90	-12	13.1	7.7
R. inferior occipital gyrus	Part of (1)	26	-92	-12	14.7	8.3
L. precentral gyrus (superior part)	19	-34	2	36	2.6	3.0*
R. precentral gyrus (superior part)	273 (2)	36	-10	48	2.9	3.1
R. precentral gyrus (inferior part)	Part of (2)	48	2	28	3.0	4.3
R. middle frontal gyrus	184	38	52	16	4.2	3.4
		40	38	28	2.8	2.7*
R. inferior frontal gyrus	39	50	18	8	2.6	3.2
L. intraparietal sulcus	50	-30	-64	44	2.9	2.9*
R. intraparietal sulcus	Part of (1)	24	-70	44	2.2	2.2*

† For details, see footnote, Table I.

* Not significant at voxel Z threshold of 3.1.

TABLE III. Foci of significant NrCBF increases in the DIS condition as compared with the FIX condition†

Activated areas	Area size	Coordinates			ΔNrCBF	Z score
		x	y	z		
L. inferior temporal sulcus	475	-42	-76	4	3.9	3.9
R. inferior temporal sulcus	1,362 (1)	42	-70	0	4.7	4.4
R. lingual gyrus	Part of (1)	20	-76	0	5.1	4.5
R. middle occipital gyrus	Part of (1)	22	-90	20	3.5	3.8
R. precentral gyrus (superior part)	115	22	-6	48	3.7	3.4
R. intraparietal sulcus	Part of (1)	20	-68	44	3.4	3.2

† For details, see footnote, Table I.

and DIS vs. FIX were performed to reveal activation, while REST vs. DIS and REST vs. FIX were performed to indicate NrCBF decreases. The stereotactic coordinates and spatial extent of the activated and deactivated areas are given in Tables I–V. Corresponding Z maps for both NrCBF increases and decreases for the 10 subjects (S1–S10) are displayed on the mean spatially normalized axial anatomical images of 5 subjects (S6–S10), for DIS vs. REST (Fig. 1), FIX vs. REST (Fig. 2), and DIS vs. FIX (Fig. 3) comparisons, respectively.

DIS vs. REST (Table I, Fig. 1)

This comparison revealed a strong, significant, and extensive occipital activation with local maxima lo-

cated bilaterally in both the inferior and middle occipital gyri. In the frontal lobe, a bilateral activation was detected in the superior part of the precentral gyrus at +40 mm (left) and +48 mm (right) above the AC-PC plane. A second focus of activation was also observed in the right inferior part of the precentral gyrus (+28 mm above the AC-PC plane). In addition, a right prefrontal activation was observed in the middle frontal gyrus. At the parietal level, bilateral activations were observed in the intraparietal sulcus.

FIX vs. REST (Table II, Fig. 2)

The main part of the areas activated during the DIS condition was also activated during the FIX condition,

TABLE IV. Foci of significant NrCBF decreases in the DIS compared to the REST condition†

Deactivated areas	Area size	Coordinates			ΔNrCBF	Z score
		x	y	z		
L. Heschl gyrus	3,434 (1)	-44	-30	12	3.4	4.7
R. Heschl gyrus	2,437 (2)	44	-30	12	3.2	5.2
L. superior temporal gyrus	Part of (1)	-52	-4	4	4.1	5.1
R. superior temporal gyrus	Part of (2)	50	2	4	2.8	3.6
L. temporal pole	Part of (1)	-44	12	-16	4.5	4.7
R. temporal pole	Part of (2)	42	14	-16	3.1	3.5
L. middle temporal gyrus	Part of (1)	-54	-62	20	3.2	3.5
R. middle temporal gyrus	105	54	-64	16	5.2	4.4
L. middle frontal gyrus	221 (3)	-36	10	48	3.0	4.1
L. middle frontal gyrus	Part of (3)	-34	20	32	3.1	3.2
L. dorsomedial frontal gyrus	409 (4)	-4	46	20	3.4	3.9
R. dorsomedial frontal gyrus	Part of (4)	12	36	40	2.6	3.0*
L. median cingulate gyrus	163	-4	-4	36	3.7	3.7
L. precuneus	785 (5)	-2	-72	28	2.8	4.0
L. posterior cingulate gyrus	Part of (5)	-12	-46	8	3.1	2.5*
R. posterior cingulate gyrus	Part of (5)	6	-58	16	2.8	3.4

† For details, see footnote, Table I.

* Not significant at voxel Z threshold of 3.1.

TABLE V. Foci of significant NrCBF decreases in the FIX condition compared to the REST condition†

Deactivated areas	Area size	Coordinates			Δ NrCBF	Z score
		x	y	z		
L. Heschl gyrus	3,360 (1)	-40	-32	8	3.9	5.1
R. Heschl gyrus	989 (2)	44	-30	12	2.1	3.7
L. superior temporal gyrus	Part of (1)	-56	-4	4	4.0	4.5
R. superior temporal gyrus	Part of (2)	50	2	4	1.4	3.6
L. temporal pole	Part of (1)	-42	4	-16	3.8	4.9
R. temporal pole	Part of (2)	44	-2	-16	3.3	4.4
L. middle temporal gyrus	Part of (1)	-54	-64	20	4.7	4.3
R. middle temporal gyrus	Part of (2)	50	-72	20	4.5	3.6
L. middle frontal gyrus	23	-54	24	20	3.9	3.1
R. superior frontal gyrus	149	22	58	-4	5.1	3.2
L. precuneus	506 (3)	-10	-58	32	3.3	3.2
R. precuneus	Part of (3)	2	-62	32	3.9	4.0

† For details, see footnote, Table I.

as compared to the REST condition. There was a strong bilateral occipital activation with local maxima located in the inferior occipital gyrus. This contrast also revealed a bilateral activation located in the superior part of the precentral gyrus at +36 mm (left) and +48 mm (right) above the AC-PC plane, whereas a second right precentral activation was detected in the inferior part of the gyrus (+28 mm above the AC-PC plane). Right prefrontal activation in the middle frontal gyrus as well as an inferior frontal activation in the pars opercularis were also found. At the parietal level, a left intraparietal sulcus and a right precuneus activation were significantly detected.

DIS vs. FIX (Table III, Fig. 3)

Taking the FIX condition as a reference, we found bilateral activation in the inferior temporal sulcus, which extended to both the middle occipital and lingual gyri in the right hemisphere (Fig. 2). Additional significant increased blood flow was found preferentially in the right superior part of the precentral gyrus as well as in the right intraparietal sulcus.

REST vs. DIS (Table IV, Fig. 1)

This comparison exhibited regions that were more active during the REST condition than during the DIS condition, thus reflecting the NrCBF decrease during the latter. The most significant NrCBF decreases during DIS as compared to REST were observed bilaterally

ally in temporal lobe. Symmetrical NrCBF decreases were observed in the transverse temporal (Heschl's) gyrus, the superior temporal gyrus, and the temporal poles. A more posterior NrCBF decrease was also detected bilaterally in the middle temporal gyrus. In the frontal lobe, the left middle frontal gyrus elicited significant NrCBF decrease, as did (bilaterally) the dorsomedial frontal gyrus. A left median cingulate NrCBF decrease was also observed. An additional NrCBF decrease was noted at the parietal level in the precuneus, extending bilaterally to the posterior cingulate gyrus.

REST vs. FIX (Table V, Fig. 2)

NrCBF decreases in the FIX condition as compared to the REST condition were similar to those reported above for the temporal lobe. In the frontal lobe, the left middle frontal gyrus as well as the most inferior part of the right superior frontal gyrus showed significant NrCBF decreases. Additional deactivations were noted bilaterally in the precuneus.

To summarize, these findings revealed a common set of bilateral cortical activations during both the simple foveal fixation (FIX condition) and the performance of the same task with peripheral distractors (DIS condition). This network was composed of the inferior and middle occipital gyri, the precentral gyrus, and the intraparietal sulcus. Additional right frontal activations were found in the prefrontal cortex, the inferior part of the precentral gyrus, and the inferior

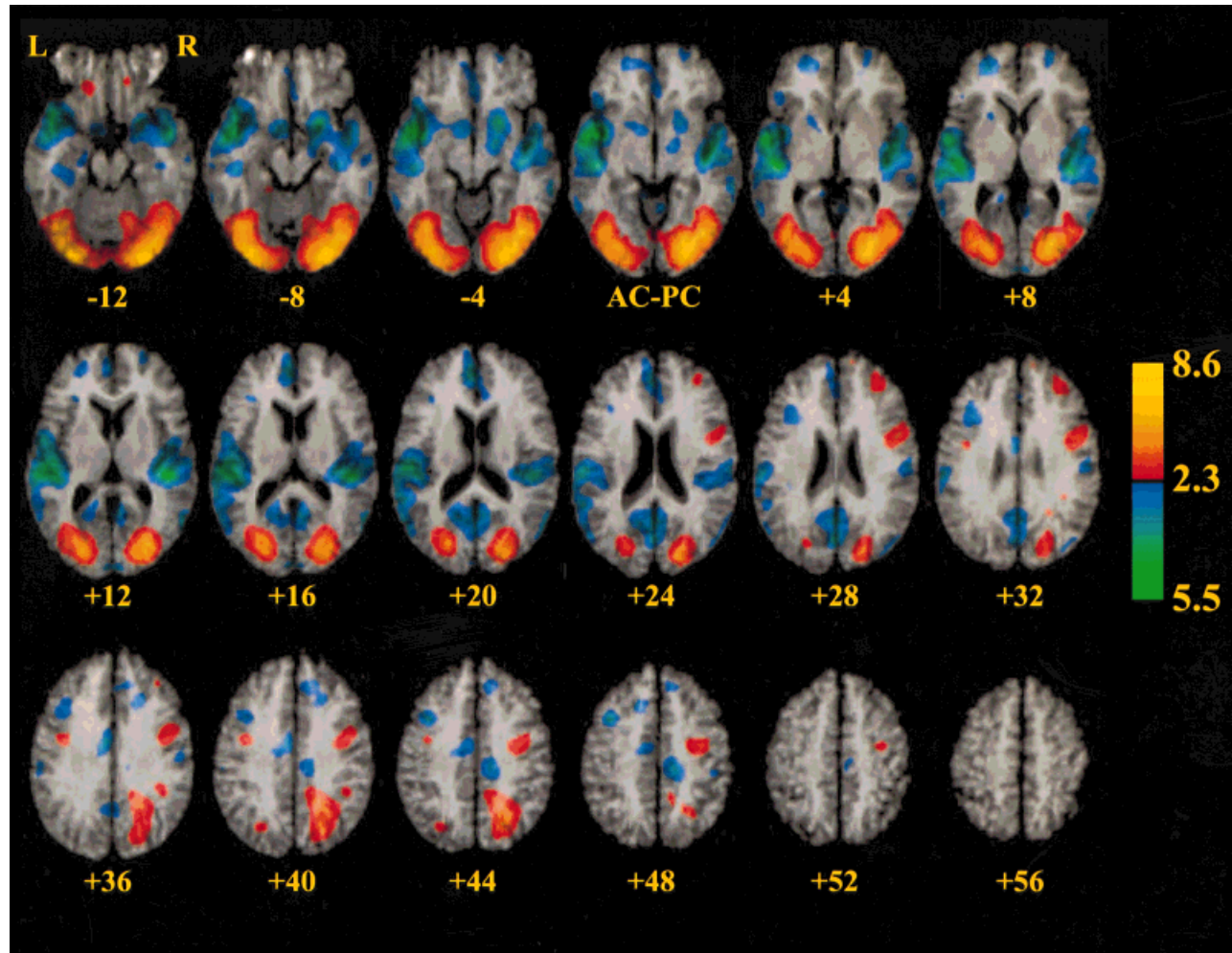


Figure 1.

SPMs corresponding to the DIS vs. REST condition comparison. Axial sections from Z maps are projected onto the mean spatially normalized axial anatomical images of 5 subjects (S6–S10). Voxels with $|Z| = 2.33$ ($P < 0.01$; not corrected for multiple comparisons) are shown. Areas showing NrCBF increases during DIS condition

are displayed in red and yellow; areas showing NrCBF decreases are displayed in blue and green. Stereotactic coordinates of local maxima and minima within the different areas are given in Tables I and IV. L, left; R, right.

frontal gyrus. Moreover, the presence of visual peripheral distractors during the foveal fixation (DIS condition) led to specific NrCBF increases in a right frontoparietal network, composed of the precentral gyrus and the intraparietal sulcus. Additional activations related to the DIS condition were observed bilaterally in the inferior temporal sulcus. Finally, NrCBF decreases were also observed during the performance of both DIS and FIX conditions. Such NrCBF decreases were centered in the superior and middle temporal gyri, the prefrontal cortex, and the precuneus and the posterior retrosplenial part of the cingulate gyrus.

DISCUSSION

In the following discussion, we shall concentrate on three main issues. First, common NrCBF increases observed during both DIS and FIX conditions will be discussed in the context of the existence of a foveal fixation system in humans and its cortical substrate. Second, the DIS vs. FIX comparison revealed distractor-related NrCBF changes within a right frontoparietal network, which will be discussed in term of the close relationship between eye movements and visuospatial attention. Third, we shall also consider the NrCBF

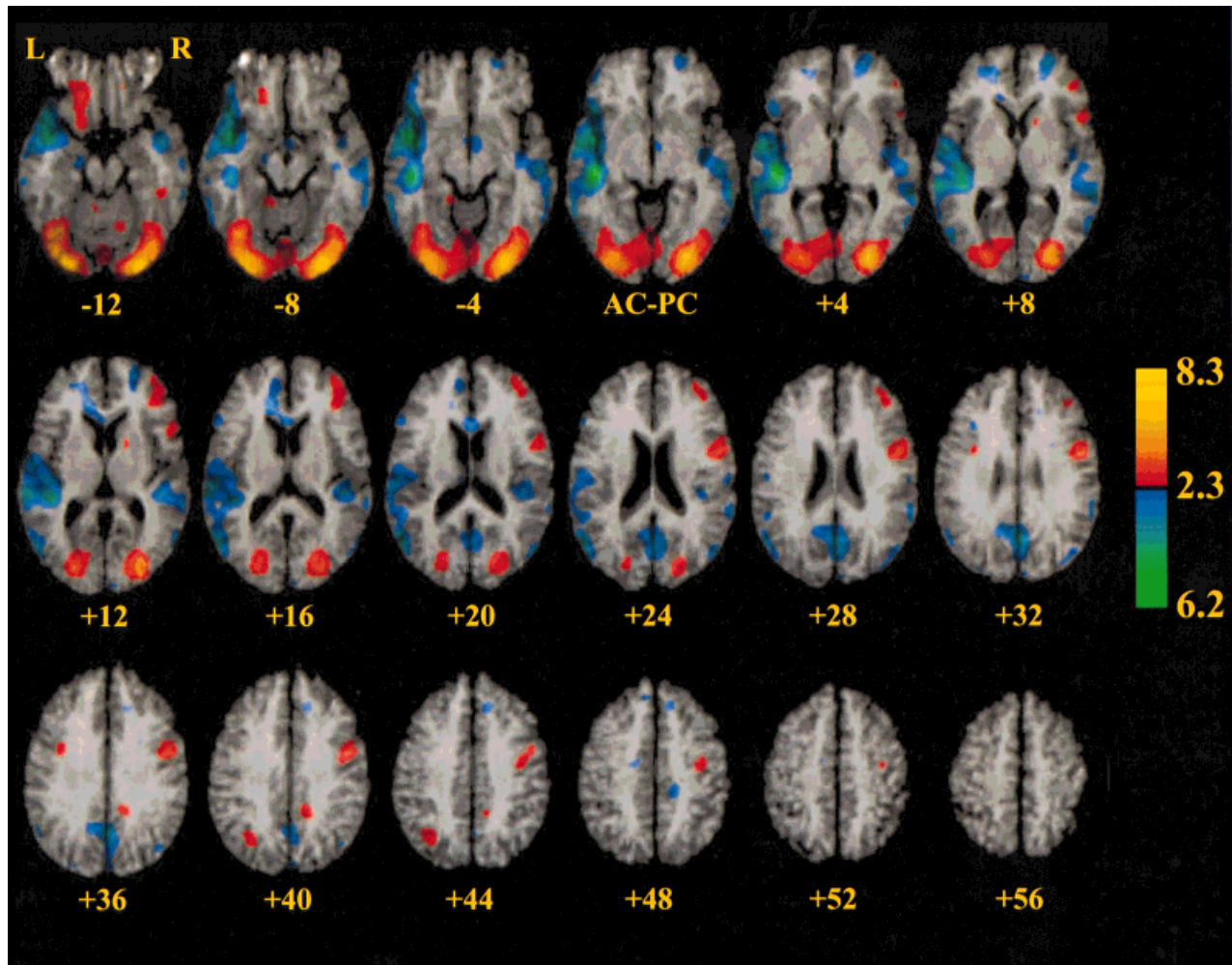


Figure 2.

SPMs corresponding to the FIX vs. REST condition comparison. Axial sections from Z maps are projected onto the mean spatially normalized axial anatomical images of 5 subjects (S6–S10). Voxels with $|Z| = 2.33$ ($P < 0.01$; not corrected for multiple comparisons) are shown. Areas showing NrCBF increases during DIS condition

are displayed in red and yellow; areas showing NrCBF decreases are displayed in blue and green. Stereotactic coordinates of local maxima and minima within the different areas are given in Tables II and V. L, left; R, right.

decreases observed during both DIS and FIX conditions as compared to the REST condition.

A human foveal fixation system

Visual occipital cortex

Relative to the REST condition, both DIS and FIX conditions evoked a significant NrCBF increase in a large part of the occipital lobe, including calcarine, medial, and lateral areas (Figs. 1, 2). These occipital activations may correspond to early visual areas, such

as V1, V2, and V3, that precede the major bifurcation of visual pathways into ventral and dorsal processing streams [reviewed in Ungerleider, 1995]. These findings agree with earlier PET studies of lateral visual association activation related to ocular fixation [Fox and Raichle, 1984; Anderson et al., 1994]. There was a more extensive activation in terms of signal amplitude and spatial extent in the visual cortex during the DIS condition than during the FIX condition, which may be due to the higher amount of visual stimulation during the DIS condition. It may also be related to a larger involvement of the selective attention to the foveal

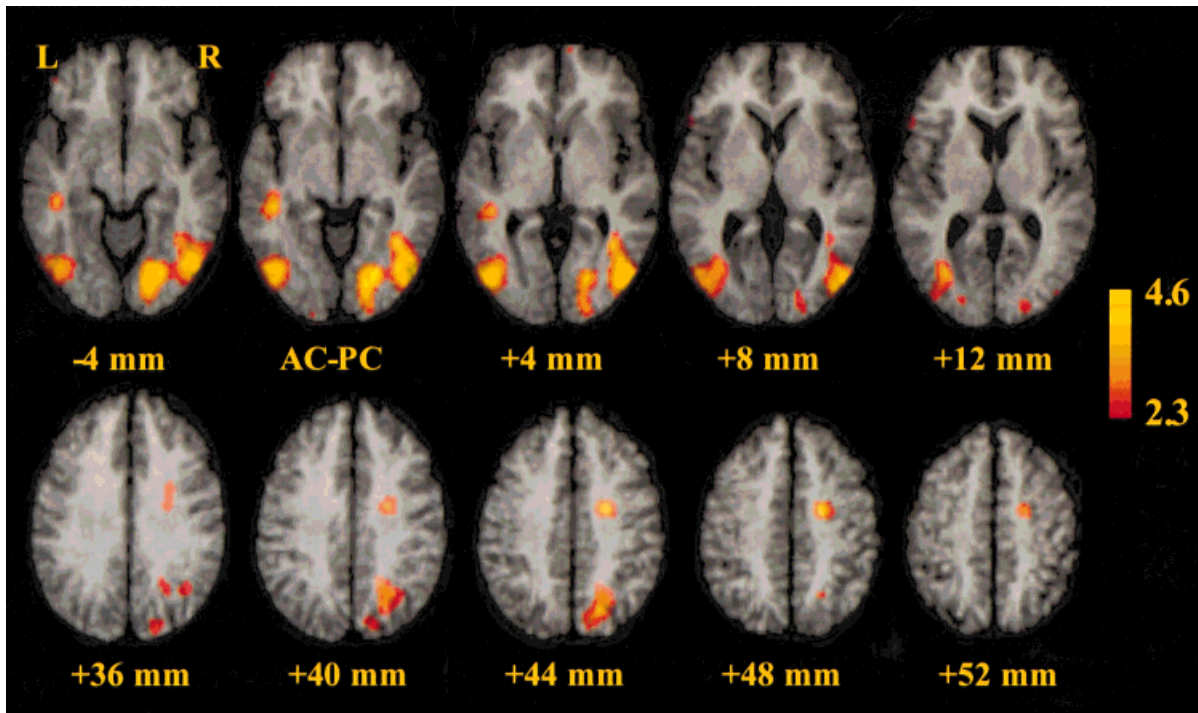


Figure 3.

SPMs corresponding to the DIS vs. FIX condition comparison. Axial sections from Z maps are projected onto the mean spatially normalized axial anatomical images of 5 subjects (S6–S10). Voxels with $|Z| = 2.33$ ($P < 0.01$; not corrected for multiple comparisons) are shown. Stereotactic coordinates of local maxima and minima within the different areas are given in Table III. L, left; R, right.

stimulus during the DIS condition, which required greater attention on the central point to inhibit reflexive eye movements towards the visual distractors. Such an explanation is consistent with previous functional imaging studies, which showed that selective attention modulates sensory responses in extrastriate regions [Corbetta et al., 1990; Pardo et al., 1990, 1991; Haxby et al., 1994; Heinze et al., 1994; Clark and Hillyard, 1996; Beauchamp et al., 1997].

Precentral gyrus (superior part)

Bilateral activations were observed in the superior part of the precentral gyrus during both DIS and FIX conditions. We also described a similar precentral activation during fixation of a recalled central target [Petit et al., 1995]. We compared the locations of the precentral local maxima in the present study and in previous functional imaging studies of various types of saccadic eye movements. Figure 4 shows that the locations of the local maxima in the superior part of the

precentral gyrus during both DIS and FIX conditions correspond well to the human FEF, as delineated by the saccade-related precentral foci. The present study extends our previous results by providing the mean location of fixation-related FEF activation within the standard stereotactic space [Talairach and Tournoux, 1988]. The coordinates (Tables I and II) localize the fixation-related FEF between the saccade-related and pursuit-related FEF activations, as recently dissociated by fMRI (Fig. 4) [Petit et al., 1997a]. This fMRI study showed a more inferior and lateral mean location of the pursuit-related region (mean Talairach coordinates $[x, y, z; n = 4]$ in left $[-39, -15, +38]$ and right $[+43, -14, +40]$ hemispheres, respectively) as compared to the location of the saccade-related region (mean Talairach coordinates $[x, y, z; n = 5]$ in left $[-30, -19, +47]$ and right $[+33, -15, +48]$ hemispheres, respectively). However, further investigations are needed to make a precise dissociation between these three oculomotor tasks, using the same methodology in the same subjects.

Stereotactic coordinates of eye movement activity in the human FEF

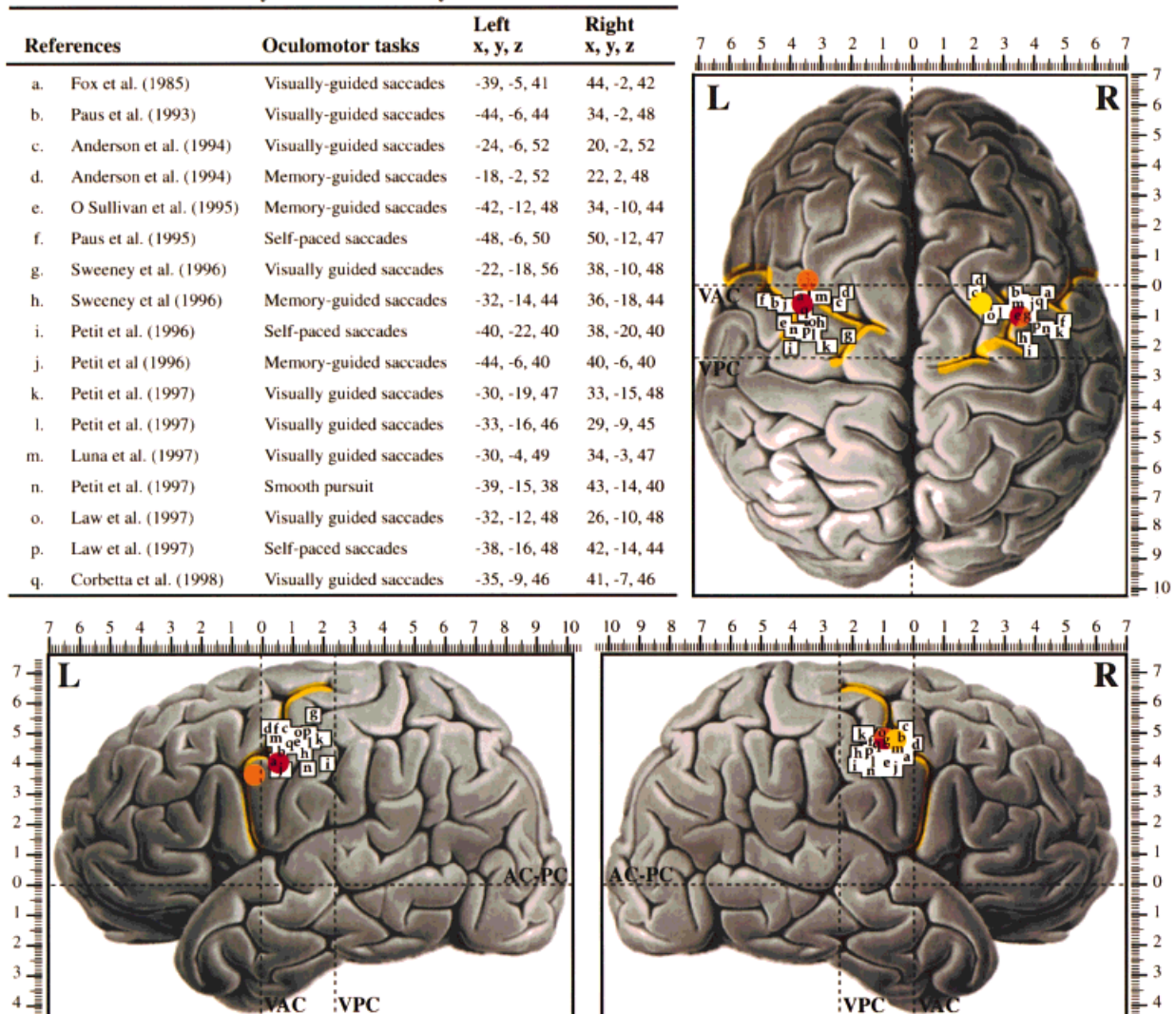


Figure 4.

Comparison of frontal eye field (FEF) activations obtained in the present study relative to previous reports. Peaks of activations were plotted onto superior (upper right) and lateral (bottom) views of a brain in standardized normalized space [Talairach and Tournoux, 1988]. The NrcBF increases detected in the superior part of the precentral gyrus are shown in red for DIS vs. REST, in

orange for FIX vs. REST, and in white for DIS vs. FIX comparisons, respectively. The numbers plot activations observed in previous studies listed at upper left. L, left; R, right; VAC and VPC, vertical plane passing through the anterior and posterior commissures, respectively.

Intraparietal sulcus

The fixation of a central point with or without the presence of visual distractors also led to a bilateral increase centered in the intraparietal sulcus (IPS) and extended to the precuneus in the right medial superior parietal gyrus (Fig. 2). The local maxima of the fixation-related IPS activations in the present study are consistent with a set of IPS activations previously

reported during different eye movement and visuospatial attention tasks (reviewed in Fig. 1 of Petit et al. [1996b] and Fig. 9 of Nobre et al. [1997]). However, the variability in location of these IPS activations in various visuospatial tasks, including eye movement studies, is important and remains an issue for further investigation. Anatomic-functional dissociation between these activated areas cannot be made at this time.

Taken together, both FEF and IPS may be part of a cortical network subserving bilaterally the foveal fixation system in humans. First, one may argue that the higher amount of visual stimulation during the FIX condition may drive visual neurons in both the FEF and the IPS and thus may induce increased NrCBF, independent of foveal fixation. However, we previously showed that NrCBF changes in FEF and the parietal cortex (angular gyrus-intraparietal sulcus) during active fixation in total darkness can be found [Petit et al., 1995]. Our findings also fit with physiological studies in the monkey showing that a group of FEF neurons discharges during a visual fixation task, this group being the second largest group of neurons that projects to the superior colliculus and the pons [Bruce and Goldberg, 1985; Goldberg et al., 1986]. Other physiological studies in the monkey described visual fixation neurons in the posterior parietal cortex, only sporadically active when the animal spontaneously looks around its surroundings, but increasing their activity abruptly with sustained fixation on a target to obtain a reward [Sakata et al., 1980; Mountcastle et al., 1975; Lynch et al., 1977]. As compared to the activity of the fixation neurons in the superior colliculus (SC), it has been proposed that the fixation-related neurons in the FEF, IPS, and SC are part of the same fixation system in the monkey [Munoz and Wurtz, 1993]. Note that the spatial resolution of the PET cameras did not allow us to observe the involvement of the superior colliculus in the present study.

Note that, contrary to previous studies [Petit et al., 1995; Law et al., 1997], no activation was found at the level of the SEF and the median cingulate gyrus during both DIS and FIX conditions. First, one may argue that this is a false-negative result, possibly related to a lower level of activation in these medial regions than for the lateral regions (e.g., FEF and IPS) involved during fixation on a central point. Another explanation of these differences may be related to the higher number of spontaneous saccades executed during the REST condition than during the fixation tasks. This may induce a saccade-related activation in these medial regions [Fox et al., 1985; Petit et al., 1993, 1996a; O'Sullivan et al., 1995; Law et al., 1997] during the REST condition, which could cancel a putative fixation-related activation during the DIS and FIX conditions.

Dorsolateral prefrontal activation

Three different foci of NrCBF increases were observed in the right frontal lobe during both DIS and FIX conditions, which may be considered as part of the anterior attentional network activated during sus-

tained and/or selective attention. Our findings are consistent with the results of previous functional imaging studies supporting a role for the right frontal lobe in the allocation of the attentional mechanisms, independent of the modality engaged [Pardo et al., 1991; Tzourio et al., 1997; Paus et al., 1997; see also Posner, 1994].

As compared with the REST condition, both DIS and FIX conditions elicited a significant NrCBF increase in the right middle frontal gyrus, corresponding mostly to area 46 as recently cytoarchitectonically redefined [Rajkowska and Goldman-Rakic, 1995]. Previous PET studies described activation of the dorsolateral prefrontal cortex (DLPFC), encompassing areas 9 and 46, during a foveal fixation task as compared with the execution of visually guided saccades [Anderson et al., 1994; Sweeney et al., 1996]. Similar DLPFC activations were also observed during antisaccade as compared to visually guided saccade performance [Sweeney et al., 1996] and during the execution of memory-guided saccades as compared to a rest condition [O'Sullivan et al., 1995]. These previous studies compared oculomotor tasks with relatively similar foveal fixation demands, which may indicate that the DLPFC activation was not directly related to foveal fixation. On the other hand, similar right DLPFC activations have been associated with short-term focusing of attention in somatosensory [Pardo et al., 1991] and auditory [Tzourio et al., 1997; Paus et al., 1997] modalities.

The right inferior part of the precentral gyrus also demonstrated an activation during both DIS and FIX conditions. Figures 1 and 2 indicate that this precentral activation extended along much of the gyrus, with a second local maxima (+28 mm above the AC-PC plane) clearly distinguishable from the FEF activation (+48 mm above the AC-PC plane). To our knowledge, no activation during fixation or other eye movements has been described previously at this level of the precentral gyrus. Recently, in a combined ERP-PET study, Tzourio et al. [1997] found that the right precentral gyrus is one of the frontal regions involved at the origin of the electrical activity during auditory selective attention [Tzourio et al., 1997]. Giard et al. [1990] also suggested that the right precentral gyrus may play a role in an orienting response and participate in setting the level of arousal in the cerebral cortex. Our results indicate that the role of the right inferior precentral gyrus is not restricted to selective attention within the auditory modality.

In addition, the pars opercularis of the right inferior frontal gyrus revealed a significant activation during the FIX condition (Fig. 2). Similar right inferior frontal activation, merging into the inferior precentral activa-

tion, was also detected during the DIS condition but failed to reach significance (NrCBF maxima coordinates [+50, +18, +8] and $Z = 1.6$). Similar intriguing activations of the right inferior frontal gyrus have also been described during a somatosensory vigilance task [Pardo et al., 1991], while listening to sentences with pseudowords [Mazoyer et al., 1993], and while forming mental imagery [Kosslyn et al., 1993]. Note that these previous studies required subjects to focus their attention within a given modality.

A right frontoparietal network for visuospatial attention

Taking the FIX condition as a reference in the DIS vs. FIX comparison made it possible to observe the perceptual and cognitive processes related to the fact that the subjects should ignore the peripheral visual distractors during the DIS condition.

First, the DIS vs. FIX comparison revealed a bilateral activation overlapping the inferior temporal sulcus. The Talairach coordinates of the local maxima (Table III) correspond to the anatomical location of the V5/MT motion-sensitive area, at the ascending limb of the inferior temporal sulcus [Watson et al., 1993]. Functional imaging studies that measured activation during perception of, or attention to, motion found similar foci [Corbetta et al., 1991; Zeki et al., 1991; Watson et al., 1993; Tootell et al., 1995; Eden et al., 1996; Barton et al., 1996]. As initially pointed out in these previous studies, the present V5/MT activation may be related to the retinal image motion elicited by the appearance of visual distractors in the periphery of the visual field during the DIS condition. In addition, Beauchamp et al. [1997] showed that both spatial and featural attention bilaterally modulate the V5/MT activation.

The DIS vs. FIX comparison also revealed distractor-related NrCBF changes within a right frontoparietal network composed of both the FEF and the IPS.

First, one may argue that the higher amount of visual stimulation during the DIS condition may drive visual neurons in both the FEF and the IPS, and thus may induce increased NrCBF independently of the foveal fixation.

Second, the presentation of the peripheral distractors would also automatically engage a shift of visuospatial attention, and both the right FEF and right IPS are likely candidates for the neural correlate of this process [Corbetta et al., 1993]. Recent functional imaging studies reappraised the anatomical loci of brain regions involved in shifts of visuospatial attention [Vandenberghe et al., 1996; Nobre et al., 1997; Corbetta, 1998; Corbetta et al., 1998]. Some attention conditions

emphasized reflexive aspects of visuospatial attention, while some others required controlled shifts of attention, and in both studies the subjects had to maintain a central eye fixation during the tasks. Equivalent patterns of brain activation, predominantly in the right hemisphere, were observed across these studies both in FEF and IPS.

In a previous study, Law et al. [1997] described NrCBF changes in FEF and IPS during fixation with or without peripheral distractors, and during overt or imagined saccadic eye movements with the same stimuli. In both regions, activity was highest during actual and imagined eye movements (shift of peripheral attention), intermediate during fixation with distractors, and lowest during simple foveal fixation. Interestingly, the fixation-with-distractors task (saccade suppression), compared to central fixation alone, revealed both FEF and IPS activation with a right-sided preponderance. Thus, in the present study, one may argue that the right frontoparietal activation is related to the necessity for subjects to inhibit a reflexive shift of visuospatial attention as well as overt eye movements.

Taken together, these previous studies support the existence of a common large-scale neural network for visuospatial attention and eye movements [Mesulam, 1981, 1990]. In such a system, a frontal component, centered around the FEF, coordinates the motor programs for exploration, scanning, reaching, and fixating, while the parietal component, centered around the IPS, provides a sensory map of the extrapersonal space. Nobre et al. [1997] showed that the loci of both precentral/premotor and superior parietal activations described in previous eye movement and visuospatial attention studies were intermingled and overwhelmingly centered around the FEF and the IPS, respectively. More recently, Corbetta et al. [1998] described a largely overlapping network of cortical regions including the FEF, SEF, and several parietal and temporal regions, which was recruited during voluntary covert shifts of attention and overt saccadic (and attentional) movements.

Both the study by Law et al. [1997] and the present work suggest that the control of reflexive shifts of visuospatial attention may result from the activity of an FEF-IPS network with a right-sided preponderance, while the direct control of eye movements may bilaterally engage such a network. Previous psychological studies showed that visuospatial attention modified the trajectories of saccadic eye movements, and the suppression hypothesis has been proposed to explain this attention-determined saccade deviation [Sheliga et al., 1994, 1995, 1997]. The suppression hypothesis

suggests that when a subject is instructed to maintain fixation and not look at the peripheral stimuli (as during the DIS condition in the present study or in a saccade suppression task [Law et al., 1997]), an imperative stimulus elicits an active inhibition of the orienting response mediated by the oculomotor structures. Shelliga et al. [1997] suggested that specific oculomotor structures, e.g., the FEF, IPS, and superior colliculus, may mediate such an inhibition by blocking reflexive eye movements. Such inhibitory processes may be part of the neurophysiological mechanisms in the right FEF-IPS network, underlying the increased effort required to maintain central fixation in the presence of peripheral distractors.

A final conclusion about the effects of visual and/or attentional factors on both FEF and IPS activations described in the present study cannot be made at this time. NrCBF changes in both FEF and IPS during the DIS condition cannot be exclusively related to the effect of visual stimuli, to active shift of covert attention, and/or to active inhibition of covert attention and overt eye movements. Voluntary covert shifts of attention and overt eye movements between extensive periods of visual fixation and sensory integration of target selection are closely integrated in everyday life and require the coordination of visual, visuomotor, and attentional signals. Corbetta et al. [1998] demonstrated that these processes recruit a common set of functional areas in the frontal (FEF, SEF), parietal (IPS), and temporal cortex, which is consistent with the hypothesis that attentional and oculomotor processes are tightly integrated at the neural level.

CBF decreases

Several recent PET studies using subtraction technique emphasized the importance of CBF decreases [Frith et al., 1991; Raichle et al., 1994; Shulman et al., 1997]. One way to conceptualize these changes is that they reflect relative neuronal activity that accompanies the reference condition as compared to the active condition. Another interpretation is that these changes may reflect deactivation of a particular region during the performance of one given task relative to another. In any case, although the physiological significance remains unclear, both DIS and FIX conditions elicited similar patterns of NrCBF decreases when compared with the REST condition.

The major result observed with respect to these NrCBF reductions was the presence of a large and symmetrical decrease centered in Heschl's gyrus, which extended to the lateral and posterior part of the superior and middle temporal gyrus. The locations of

these local minima correspond to both primary and association auditory cortices, usually described as an activation in functional imaging studies with nonlinguistic auditory stimuli [Lauter et al., 1985; Zatorre et al., 1992; Binder et al., 1994; Tzourio et al., 1997]. Moreover, similar NrCBF reductions in the auditory cortex were reported using PET and fMRI during visual matching tasks [Haxby et al., 1994; Clark et al., 1996] and visual working memory tasks [Courtney et al., 1996]. Previous PET studies also revealed that attention to visual stimuli may be associated with suppression of neural activity in areas that process input from unattended sensory modalities [Lauter et al., 1985; Haxby et al., 1994; Drevets et al., 1995; Mellet et al., 1996]. In the current study, NrCBF temporal decreases during foveal fixation relative to the baseline condition may also reflect a form of cross-modality inhibition [Posner and Dehaene, 1994].

The locations of the temporal NrCBF reductions also correspond to those described as activations in functional imaging studies with auditory stimuli for language-related processing [reviewed in Mazoyer et al., 1993; Fiez et al., 1996; Zatorre et al., 1996; Fletcher et al., 1995; Shulman et al., 1997]. On the other hand, NrCBF decreases have been demonstrated in the visual associative cortex during passive listening to word lists [Mellet et al., 1996]. The present temporal NrCBF decreases also include the temporal pole bilaterally (Figs. 1, 2), a putative region for auditory working memory during speech processing [Mazoyer et al., 1993]. Taken together, these previous reports and the present study showed that an active condition which implicates visual processing induces NrCBF increases in vision-related areas and NrCBF decreases in language-related areas. Such a functional duality is supported by the assumption that verbal and visual representations are different cognitive entities [Kawashima et al., 1995].

The precuneus and the posterior cingulate gyrus also showed a bilateral significant NrCBF decrease. The present findings are consistent with other PET studies that described similar NrCBF reductions in these retrosplenial regions as the consequence of a blood flow increase during the rest condition [Buckner et al., 1995, 1996; Mellet et al., 1996; Fiez et al., 1995; Shulman et al., 1997; Tzourio et al., 1997].

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